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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/660,301 Customer No. 23379

Inventors: Giroir et al. Confirmation No. 5400

Filed: Sep 10, 2003 Group Art Unit: 1644

Docket No. UTSD:1477 Examiner: Chun Crowder

Title: *Macrophage Migration Inhibitory Factor as a Marker for Cardiovascular Risk*

CERTIFICATE OF TRANSMISSION
I hereby certify that this corr is being transmitted by facsimile to the Comm for Patents at 571-273-8300 on August 14, 2006.

Signature _____
Richard Aron Osman

BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Honorable Board:

We appeal from the Jul 14, 2006 Examiner's final rejection of claims 1 - 19.

REAL PARTY IN INTEREST

The real party in interest is the Board of Regents, the University of Texas System, the assignee of this application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF CLAIMS

Claims 1 - 19 are rejected and subject to this appeal.

STATUS OF AMENDMENTS

The Advisory Action dated 08/09/06 indicated that our Amendment filed Jul 18, 2006 would be entered for purposes of appeal. All Amendments are believed to be properly before the Board.

SUMMARY CLAIMED SUBJECT MATTER

Well-known indicia of cardiovascular risk include age, sex, smoking, systolic blood pressure and total cholesterol. In addition, several biochemical markers of cardiovascular health risk have been proposed, including C-reactive protein (CRP), B-type natriuretic peptide (BNP), sialic acid, etc. Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine/hormone that has been associated with a number of disease states, including sepsis, prostate cancer, aneurysmal expansion, acute myocardial infarction, atherosclerosis, diabetes, etc. We have determined that the serum level of MIF is extremely elevated in patients with high cardiovascular risk, and that it falls rapidly when interventions are made which reduce this risk. Prior to our work, MIF levels have never been associated with cardiovascular risk in non-diseased or non-diagnosed persons. Like CRP, MIF is a marker of cardiovascular risk providing clinically important prognostic information in the assessment of overall cardiovascular risk. (Specification, p.1, line 12 - p.2, line 2).

The claimed subject matter includes a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease, the method comprising the step of: determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, and wherein the method further comprises a step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay (claim 1; Specification, p.3, lines 14-20).

Dependent claims recite this method further comprising the step of assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration (claim 2); further comprising the step of prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration (claim 3); further comprising making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an

LDL assay (claim 4); wherein the detecting step is repeated over time intervals to monitor change in cardiovascular risk for the person over time; and wherein the detecting step is repeated over treatment to monitor change in cardiovascular risk for the person over treatment (claim 5).

The claimed subject matter also includes a method for characterizing a risk of developing a future cardiovascular disorder in an apparently healthy individual, the method comprising steps: obtaining a test MIF level in the blood, saliva or urine of the individual; comparing the test MIF level to a predetermined control MIF value; and characterizing the individual's risk of developing the future cardiovascular disorder based upon the test MIF level in comparison to the predetermined control MIF value (claim 7).

Dependent claims recite this method wherein the predetermined control MIF value is a plurality of predetermined MIF level ranges and the comparing step comprises determining in which of the predetermined MIF level ranges the individual's test MIF level falls (claim 8); wherein the individual is apparently healthy but statistically overweight or obese (claim 9); wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction (claim 10); wherein the test MIF level is compared to the predetermined control MIF value to establish a first risk value, and the method further comprises the steps of: obtaining a test cholesterol level in the individual; comparing the test cholesterol level to a predetermined control cholesterol value to establish a second risk value; and characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk value different from said first and second risk values (claim 11); wherein the predetermined control MIF value is a first plurality of predetermined MIF concentration ranges and the comparing step comprises determining in which of the predetermined MIF concentration ranges the individual's test MIF level falls (claim 12); wherein the individual is apparently healthy but statistically overweight or obese (claim 13); wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction (claim 14)

The claimed invention also includes a method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder, the method comprising steps: obtaining a test MIF level in the blood, saliva or urine of the individual; and comparing the test MIF level to a predetermined control MIF value, wherein

the test MIF level in comparison to the predetermined control MIF value is indicative of whether the individual will benefit from treatment with said agent (claim 15).

Dependent claims recite this method wherein the predetermined control MIF value is a plurality of predetermined MIF concentration ranges and the comparing step comprises determining in which of the predetermined MIF concentration ranges the individual's test MIF level falls (claim 16); wherein the individual is apparently healthy but statistically overweight or obese (claim 17); wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction (claim 18); and wherein the agent is aspirin (claim 19).

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

I. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 1 - 19 UNDER 35USC112, FIRST PARAGRAPH (WRITTEN DESCRIPTION).

II. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIM 1 UNDER 35USC102(B).

ARGUMENT

I. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1 - 19 UNDER 35USC112, FIRST PARAGRAPH (WRITTEN DESCRIPTION).

The Action objects to the words "test" and "control". As recently restated by the Federal Circuit:

> In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." [cites omitted]
> All Dental Prodx, LLC v. Advantage Dental Prods, Inc., 309 F.3d 774, 779 (Fed. Cir. Oct 2002).

The invention is a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease by determining the MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person. The concept of a "marker of cardiovascular risk" implies to one skilled in the art that the marker is different in the risk group and in a corresponding control group. Furthermore, what you call the

measure from the examined person ("test", "subject", etc.) and what you call the compared-to measure ("control", "predetermined value", etc.) are arbitrary and self-evident, inherent measures required for a disease "marker":

> The invention provides methods for characterizing an apparently healthy individual's risk of, and/or developing their risk profile for developing a future subject cardiovascular disorder. The method comprises obtaining a level of MIF in the individual, typically expressed as MIF concentration, and comparing the level of the marker to a predetermined value. The individual's risk or risk profile of developing a future subject cardiovascular disorder then is characterized based upon the level of the marker in comparison to the predetermined value. Specification, p.3, lines 14-20.

The recited predetermined value is a control:

> The predetermined value will depend upon the characteristics of the patient, and/or the relevant patient population. The predetermined value can be a single value, multiple values, a single range or multiple ranges. Thus, in one embodiment, the predetermined value is a plurality of predetermined marker level ranges, and the comparing step comprises determining in which of the predetermined marker level ranges the individual's level falls. In another embodiment, the predetermined value is a historical value from the patient. Specification, p.4, lines 11-16.

Though not required, the Specification even expressly refers to the compared-to or "predetermined value" a "control":

> I. Comparison of MIF and CRP levels as correlates to reductions in cardiovascular risk. This study was designed to compare MIF and CRP as markers correlating with cardiovascular risk.
>
> Methods: In an initial demonstration, we monitored MIF in obese adults, with very high cardiovascular risk, who were subjected to a one-year regimen of diet and exercise.
>
> Results: We found that MIF levels tracked progress (reduction in cardiovascular

risk) through the treatment regimen better than did CRP. In our ***control*** group (n=83), MIF levels were 38 +/- 16 ng/ml. The obese patients at baseline are elevated to 100+ ng/ml generally and drop to normal levels generally after 1 year. Specification, p.5, line 7 (emphasis added)

That the determined MIF concentration is a "test", and the compared-to value is a "control" is both self-evident and inherent in the original claims. The issue for Written Description is whether the Specification reasonably conveys possession of the invention as claimed to those skilled in the art, and there is no evidence or argument of record that it fails to convey that possession.

II. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIM 1 UNDER 35USC102(b).

Yabanuka et al. (Diabetes Care 2000, 23; 2, 256-58) "examined the concentration of serum MIF in type 2 diabetes to clarify the possibility that MIF is associated with the disregulation of glucose metabolism." p.256, sentence bridging cols. 1, 2 .

The authors report mixed findings: "The serum MIF level was elevated as the clinical stage of diabetic retinopathy advanced, but that was low in the proliferatiive stage (Fig.2). The serum MIF did not differ with the clinical stage of diabetic nephropathy and neuropathy." p.256, col.3, lines 16-22.

The authors speculate on possible explanations: "It is speculated that MIF stimulates insulin secretion and MIF secretion is regulated by glucose. It may be reasonable that MIF seems to modulate the carbohydrate metabolism as MIF modulates the inflammatory and immunological responses, counterregulating impaired homeostasis by the action of glucocorticoid suppression." p.257, col.2, lines 81-6.

The authors conclude that MIF is not a specific disease marker, but a nonspecific marker for illness in general: "Increased serum MIF may be another nonspecific marker for illness in general, rather than a key player in the pathogenesis of type-2 diabetes. In fact, MIF was increased in the sera of patients with uveitis and atopic dermatitis.... p.257, col.3, lines 12-17.

Claim 1 recites a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease. The claim requires at least two steps: a

first step of determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk; and a second step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

Yabanuka et al. neither teach nor suggest the claimed two-step method. Yabanuka et al. do not suggest that MIF is a marker for cardiovascular risk. To the contrary, they suggest it is not useful as any specific disease marker, but rather is a non-specific marker for illness in general. The Action suggests anticipation of claim 1 wherein the second step is (a) "assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration" (Action, p.4, last line); however, Yabanuka et al. nowhere teach or suggest assaying MIF as a marker for cardiovascular disease, and nowhere teach or suggest assaying MIF as a marker for cardiovascular disease, and then assigning to the subject person a cardiovascular risk metric in accordance with the assayed MIF concentration. Since Yabanuka does not teach or suggest assigning a cardiovascular risk metric in accordance with an assayed MIF concentration, the reference can not anticipate our claim.

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals. The appeal brief fee is provided in the attached PTO-2038. We authorize charging our Deposit Account No.19-0750 for any necessary fee or extension of time (order UTSW:1477).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

No related proceedings are known to exist.

CLAIMS APPENDIX

1. A method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease, the method comprising the step of:

determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, and wherein the method further comprises a step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

2. The method of claim 1, further comprising the step of assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration.

3. The method of claim 1, further comprising the step of prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration.

4. The method of claim 1, further comprising making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

5. The method of claim 1, wherein the detecting step is repeated over time intervals to monitor change in cardiovascular risk for the person over time.

6. The method of claim 1, wherein the detecting step is repeated over treatment to monitor change in cardiovascular risk for the person over treatment.

7. A method for characterizing a risk of developing a future cardiovascular disorder in an

apparently healthy individual, the method comprising steps:

obtaining a test MIF level in the blood, saliva or urine of the individual,

comparing the test MIF level to a predetermined control MIF value, and

characterizing the individual's risk of developing the future cardiovascular disorder based upon the test MIF level in comparison to the predetermined control MIF value.

8. The method of claim 7, wherein the predetermined control MIF value is a plurality of predetermined MIF level ranges and the comparing step comprises determining in which of the predetermined MIF level ranges the individual's test MIF level falls.

9. The method of claim 7, wherein the individual is apparently healthy but statistically overweight or obese.

10. The method of claim 7, wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction.

11. The method of claim 7, wherein the test MIF level is compared to the predetermined control MIF value to establish a first risk value, and the method further comprises the steps of:

obtaining a test cholesterol level in the individual,

comparing the test cholesterol level to a predetermined control cholesterol value to establish a second risk value, and

characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk value different from said first and second risk values.

12. The method of claim 11, wherein the predetermined control MIF value is a first plurality of predetermined MIF concentration ranges and the comparing step comprises determining in which of the predetermined MIF concentration ranges the individual's test MIF level falls.

13. The method of claim 11, wherein the individual is apparently healthy but statistically

overweight or obese.

14. The method of claim 11, wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction.

15. A method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder, the method comprising steps:

obtaining a test MIF level in the blood, saliva or urine of the individual, and

comparing the test MIF level to a predetermined control MIF value,

wherein the test MIF level in comparison to the predetermined control MIF value is indicative of whether the individual will benefit from treatment with said agent.

16. The method of claim 15, wherein the predetermined control MIF value is a plurality of predetermined MIF concentration ranges and the comparing step comprises determining in which of the predetermined MIF concentration ranges the individual's test MIF level falls.

17. The method of claim 15, wherein the individual is apparently healthy but statistically overweight or obese.

18. The method of claim 15, wherein the cardiovascular disorder is selected from the group consisting of stroke and myocardial infarction.

19. The method of claim 15, wherein the agent is aspirin.